Hydroxyurea

Hydroxyurea is indicated for use in the treatment of certain malignancies and in sickle cell anemia, and has been used investigationally for the treatment of HIV. Its potential safety and effectiveness for treatment of HIV have not been established, and clinicians should be aware of important safety precautions regarding its use. Hydroxyurea does not have direct antiretroviral activity; rather, it inhibits the cellular enzyme ribonucleotide reductase, resulting in reduced intracellular levels of deoxynucleoside triphosphates (dNTPs) that are necessary for DNA synthesis. Depletion of the dNTP pool results in arrest of the cell cycle in the G1 phase prior to DNA synthesis; in an HIV-infected cell, incomplete reverse transcription of the viral genome also results from depletion of the dNTP pool *[1]*. Hydroxyurea preferentially depletes intracellular dATP; therefore, it has been hypothesized that the antiretroviral activity of ddI and d4T may be enhanced in combination with hydroxyurea. Hydroxyurea also induces the activity of cellular kinases that phosphorylate nucleoside analogue reverse transcriptase inhibitors, potentially further enhancing their antiretroviral activity.

Few data are available from controlled clinical trials that provide support for the clinical utility of hydroxyurea as an adjunct in the treatment of HIV infection. In limited studies, the addition of hydroxyurea to a regimen of ddI +d4T or ddI alone appeared to result in moderately enhanced antiretroviral activity *[2-4]*, although the optimal dosage and dosing schedule were not determined. In contrast, in ACTG 5025, a randomized, controlled clinical trial conducted in subjects on potent antiretroviral therapy with levels of plasma viremia <200 copies/mL *[5]*, no statistically significant differences in viral load suppression were observed in patients receiving hydroxyurea 600 mg twice daily in combination with ddI+d4T+indinavir compared to those receiving the combination regimen without hydroxyurea. Importantly, this trial was prematurely closed due to higher rates of drug toxicity in patients randomized to the hydroxyurea-containing arm. Among 68 patients randomized to hydroxyurea, three deaths related to complications of pancreatitis were reported, and a substantial decrease in median $CD4^+$T cell count was observed in the hydroxyurea treatment group. The increased frequency of fatal pancreatitis in the hydroxyurea-containing arm was not statistically significant and had not been reported previously. These cases of fatal pancreatitis do, however, raise the question of whether hydroxyurea in combination with ddI+d4T may increase the risk of ddI-associated pancreatitis. Additional concerns regarding the use of hydroxyurea in HIV infection have been raised in this trial and other studies, and include an increased risk of persistent cytopenias *[6]* and hepatotoxicity *[7]*, the drug's teratogenic properties, and the possibility of an increased risk of neuropathy. Given these concerns, more data on the potential safety and efficacy of lower doses of hydroxyurea are necessary to determine if hydroxyurea in combination with antiretroviral agents has a therapeutic role for HIV infection. Clinicians considering the use of hydroxyurea in a treatment regimen for HIV should be aware of the limited and conflicting nature of data in support of its efficacy, and the importance of monitoring patients closely for potentially serious toxicity (DII).

References

1. Rutschmann OT, Opravil M, Iten A, et al. A placebo-controlled trial of didanosine plus stavudine, with and without hydroxyurea, for HIV infection. The Swiss HIV Cohort Study. *AIDS*, 1998. 12(8): p. F71-7.
2. Montaner JS, Zala C, Conway B, et al. A pilot study of hydroxyurea among patients with advanced human immunodeficiency virus (HIV) disease receiving chronic didanosine therapy: Canadian HIV trials network protocol 080. *J Infect Dis*, 1997. 175(4): p. 801-6.
3. Gao WY, Cara A, Gallo RC, Lori F. Low levels of deoxynucleotides in peripheral blood lymphocytes: A strategy to inhibit human immunodeficiency virus type 1 replication. *Proc Natl Acad Sci U S A*, 1993. 90(19): p. 8925-8.
4. Federici ME, Lupo S, Cahn P, et al. Hydroxyurea in combination regimens for the treatment of antiretroviral-naive HIV-infected adults. 12th World AIDS Conference. Geneva, 1998. (Abstract 12235).
5. ACTG 5025 Team, *Closure of ACTG 5025*. 1999.
6. Goodrich J, Khardori N. Hydroxyurea toxicity in human immunodeficiency virus-positive patients. *Clin Infect Dis*, 1999. 29(3): p. 692-3.
7. Weissman SB, Sinclair GI, Green CL, Fissell WH. Hydroxyurea-induced hepatitis in human immunodeficiency virus-positive patients. *Clin Infect Dis*, 1999. 29(1): p. 223-4.